The Sjögren-Mikulicz Syndrome

Its Relationship to Connective Tissue Disorders

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• **Sjögren-Mikulicz syndrome, formerly thought rare, is recognized with increasing frequency, especially in middle-aged and elderly women. Often in the past, because of the peculiar swelling of the parotid gland which is a feature of the disease, the gland was removed on suspicion of cancer. New tests can identify cases in which the swelling is a part of the Sjögren-Mikulicz syndrome. In those cases the enlargement may disappear spontaneously or after treatment with corticosteroids. The tests consist chiefly of examining both the quality and the quantity of tears secreted; and in some cases biopsy of the gland may be necessary.**

The syndrome appears so often together with rheumatoid arthritis and related diseases as to give indication that it may be related etiologically. The cause is unknown. One possibility is that the patients form antibodies to their own glandular products, which destroy those products.

WITHIN THE LAST FEW YEARS Sjögren's syndrome and Mikulicz' syndrome, previously believed to be two separate entities, have come to be recognized as a single, combined syndrome significantly related to rheumatoid arthritis as well as to other connective tissue diseases.

That the entity is more common than was formerly supposed is attested by the several large series of cases recently assembled,[5,16] which have brought the number of reported cases to over a thousand, and by the fact that, when properly tested for, its ocular manifestations have been found to be the most frequent type of eye involvement in rheumatoid arthritis.[16,17]

Sjögren's Syndrome (Sicca Syndrome). A detailed description of Sjögren's syndrome has been available in the ophthalmological literature since 1933.[14] The condition is characterized by dryness of the nose, mouth, throat and vagina; by a decrease in the quantity of tears, and, as demonstrated electrophoretically, by deficiency of lysozyme in the tears.[7] This enzymatic deficiency occurs early; it may precede the decrease in quantity of tear production. As tear secretion progressively diminishes, abnormalities develop in the epithelium of the cornea and conjunctiva. At this stage, known as *keratoconjunctivitis sicca,* small punctate defects occur in the cornea, characteristically in its lower half. When the disease becomes far advanced, *filiform keratitis* ensues: Epithelial threads, often in the form of spiral filaments, are attached at one end to the cornea and float freely at the other.

Mikulicz' Syndrome. Considerable confusion has existed regarding the nature of nonsuppurative relapsing parotid swellings since Mikulicz recorded the first such case in 1892. During the years that followed, a variety of unrelated conditions causing enlargement of the parotid glands were grouped together under the name *Mikulicz' syndrome,* with no regard to the histopathologic features in the gland. Within the past decade Morgan and Castleman[9] defined the changes in the parotid gland of patients with Mikulicz' syndrome. When such diverse entities as Boeck's sarcoid, lymphoma and tuberculosis were excluded, the histologic features in Mikulicz' syndrome were seen to be unique. They consisted of diffuse infiltration with lymphocytes and pronounced alteration of the ducts. Small islands (epimyoepithelial islands) were formed, containing altered ductal material, and were characterized by hyalinization and fibrosis (Figure 1). When the clinical features of these cases were reviewed,[8] it was observed that in many of the patients the eyes and mucous membranes had been dry; in a number of instances, the diagnosis of keratoconjunctivitis sicca had been made.

The Combined Sjögren-Mikulicz Syndrome. Because patients who complain primarily of dry eyes (Sjögren's syndrome) often also have parotid enlargement, and because patients with parotid swelling (Mikulicz' syndrome) frequently have dry eyes, the identity of the two syndromes is suggested. When it is recalled that the pathologic findings in the parotid glands of both groups of patients are the same, and inflammatory joint disease is common to both groups of patients,[8] Sjögren's syndrome and Mikulicz' syndrome merge into one entity. Failure

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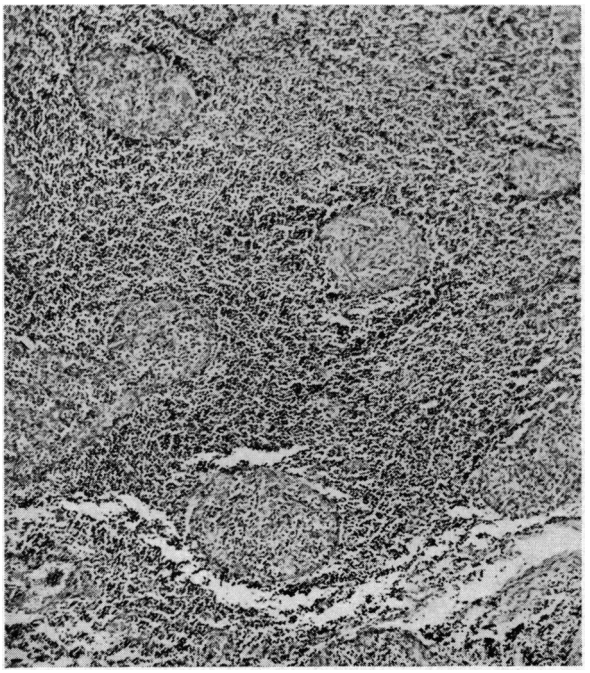

Figure 1.—Photomicrograph of section of parotid gland, showing many epimyoepithelial islands containing altered ductal tissue and hyaline material surrounded by massive lymphocytic infiltration (×100).

to recognize their identity in the past had stemmed from the fact that many cases, especially in the earlier stages, represented a *forme fruste* or an incomplete syndrome—in some it was parotid enlargement that was noticed first; in others it was the ocular complication. However, as the disease progressed, the entire triad of mucosal and ocular dryness, parotid enlargement and arthritis would often appear.

In its fully developed form the combined syndrome consists of dryness and atrophy of the conjunctiva, cornea, buccal and nasal mucosa, tongue, throat and vagina, and hyposecretion of the gastric and other exocrine glands. Recurrent nonsuppurative parotitis is frequently present. Arthritis is a usual feature of the disease. The condition mainly affects older women, and familial occurrences have been observed.

RELATIONSHIP TO THE CONNECTIVE TISSUE DISEASES

Arthritis. Sjögren[15] found objective evidence of arthritis in 64 per cent of patients who had the syndrome that bears his name. Other investigators, employing the rigid criteria for the diagnosis of rheumatoid arthritis established by the American Rheumatism Association, have confirmed the frequent incidence of rheumatoid arthritis in patients with the sicca syndrome.[3] The presence of positive rheumatoid reactions to serologic tests in as many as 95 per cent of patients with the syndrome has further demonstrated this intimate relationship.[1] When patients in an arthritis clinic were screened for keratoconjunctivitis sicca by means of the rose bengal test, a positive diagnosis was made in more than 14 per cent.[5] Keratoconjunctivitis sicca was found in as many as 34 per cent of patients with advanced rheumatoid arthritis.[17] When one considers that rheumatoid arthritis is widespread among the general population, it is apparent that the Sjögren-Mikulicz syndrome can no longer be considered an uncommon clinical problem.

Other Connective Tissue Disorders. Because rheumatoid arthritis resembles the other diseases that primarily affect connective tissue, it is plausible to expect that the Sjögren-Mikulicz syndrome would appear in these diseases as well. In 1952, Pirofsky and I reported recurrent nonsuppurative parotitis in three of 34 patients with systemic lupus erythematosus;[13] more recently, in reviewing a group of 83 patients with systemic lupus erythematosus[11] for the presence of parotitis, it was seen in 7 per cent. When patients with Sjögren's syndrome were investigated for systemic lupus erythematosus, the LE phenomenon was observed in more than 35 per cent.[4]

Sjögren-Mikulicz syndrome also occurs in scleroderma, an association recently reviewed by the author[12] and since reported by other observers.[1,16] It has been noted, but only rarely, in polyarteritis.[2,10,16]

ETIOLOGY

The close association between Sjögren-Mikulicz syndrome and connective tissue disorders suggests a pathogenic link between them. The frequent incidence of abnormal serologic reactions in patients with the Sjögren-Mikulicz syndrome is reminiscent of the abnormalities in immune reactions and in serum proteins displayed by the connective tissue disorders. Bloch and associates[1] found hypergammaglobulinemia in 71 per cent, positive reaction to the Coombs test in 25 per cent, and thyroglobulin antibodies in 14 per cent. The striking similarity between the pathologic changes in the parotid gland in Sjögren-Mikulicz syndrome and those in the thyroid gland in Hashimoto's disease has suggested that an autoimmune mechanism may operate in the Sjögren-Mikulicz syndrome. This hypothesis is strengthened by the occasional demonstration of antibodies to extracts of lacrimal and salivary glands in the blood of patients with the syndrome.[6] Although at this stage of knowledge much regarding pathogenesis is still unclear, the immunologic approach appears to be most promising.

Figure 2.—Schirmer test—a measure of tear secretion.

DIAGNOSIS

Although all features of the combined syndrome may not be manifest, particularly in the early stages of disease, appropriate diagnostic tests should be performed in any patient with dryness of the eyes and mucosal surfaces, or idiopathic enlargement of the parotid gland, especially when noted in conjunction with arthritis. The tests, which are in the main simple and readily available, are as follows:

Tests for Ocular Manifestations. The quantity of tears produced may be measured by means of Schirmer's test (Figure 2). Filter paper of standard size is inserted under the lower lids. The normal subject wets 15 mm. of the paper in five minutes; patients with the Sjögren-Mikulicz syndrome will wet less than that. In advanced cases the test paper may remain completely dry. This is a screening test, and may occasionally give false-positive responses, especially in elderly persons, but one can be relatively confident if only 5 mm. or less of the paper is wet in the given time.

The electrophoresis of tears represents a more precise test of lacrimal secretion. There is decrease or absence of lysozyme in the tear fluid as an early and constant finding in keratoconjunctivitis sicca. Unfortunately this valuable test is limited because it requires special equipment and technical skill.

The punctate defects in the cornea designated as "keratoconjunctivitis sicca" may be discerned through a slit lamp after instillation of a 1 per cent solution of fluorescein. Fluorescein paper strips may also be employed, and if a slit lamp is not available a magnifying glass may be used.

Instillation of rose bengal dye is an alternative to slit lamp examination. Cautious interpretation is necessary since in sensitive persons the dye itself occasionally causes epithelial trauma. Topical anethesia beforehand is advisable to avert pain. A positive reaction to the rose bengal test is intense staining of the conjunctiva. Red triangles appear with their bases toward the cornea, filling the palpebral aperture (Figure 3). In earlier stages of disease, staining may be limited to irregular discontinuous areas of the conjunctiva. These are not diagnostic; they are occasionally seen in apparently normal subjects.

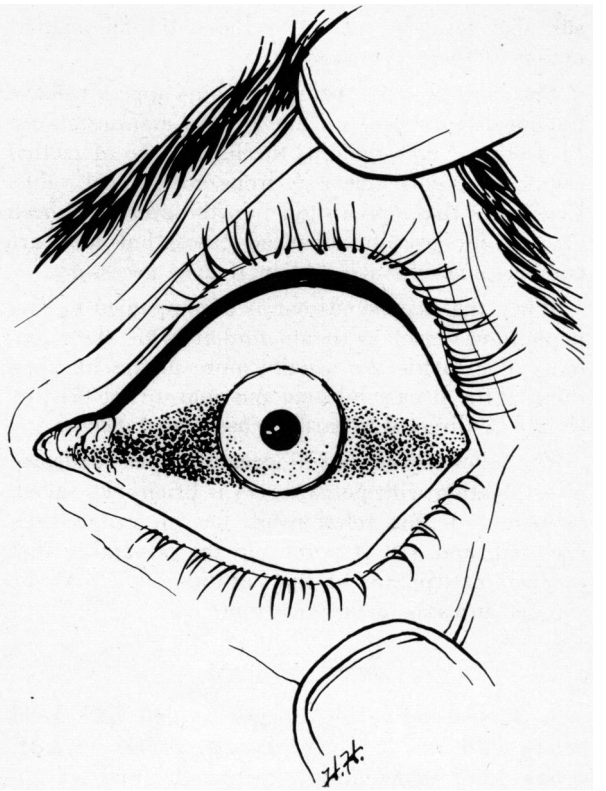

Figure 3.—Appearance of the eyes (with rose bengal solution) in keratoconjunctivitis sicca.

In a small proportion of patients filiform keratitis develops as a late complication of the disease. This can be diagnosed with a corneal microscope by the characteristic appearance of the filiform epithelial threads. One should not wait for this advanced sign before making the diagnosis of Sjögren-Mikulicz syndrome.

Test for Parotid Gland Manifestations. Enlargement of the parotid gland often suggests neoplasm, and may lead to parotid extirpation with its risk of facial palsy. The diagnosis of Sjögren-Mikulicz syndrome as the cause of the enlargement may be confirmed by biopsy. Punch biopsy of the parotid has been used successfully, but surgical biopsy appears to be the safer procedure.

THERAPY

Treatment for the parotid enlargement is seldom necessary, since the gland frequently subsides spontaneously. In some cases the administration of steroids is followed by prompt detumescence, a re-

sult that may be related to the anti-inflammatory action of these compounds.

Parenterally administered steroids appear to have no consistent effect on the ocular manifestations. Protective eyeglasses plus the liberal use of methyl cellulose or cortisone eye drops are of real value. Eyeglasses that squirt fluid into the eyes have been devised for use in advanced cases, but they are cumbersome and are seldom if ever necessary.

When the sicca syndrome is accompanied by systemic illness, such as rheumatoid arthritis, the symptoms of arthritis are usually more distressing than those of the sicca syndrome and appropriate therapy should be directed toward the associated disease.

The following case of Sjögren-Mikulicz syndrome in association with polyarteritis is briefly described, because (1) this relationship has so rarely been reported, and (2) it points up the possibility that surgical extirpation of the parotid gland may be avoided in cases of this syndrome.

REPORT OF A CASE

A 36-year-old white housewife had had good health until age 26 when bilateral parotid swelling, severe joint pains, fever, adenopathy and splenomegaly developed. Results of laboratory tests showed moderate normochromic anemia and a biologically false-positive serological reaction. The symptoms subsided after one week in hospital and the patient remained well for two years. Then the left parotid enlargement recurred. Because of suspicion of a parotid tumor, the gland was removed. Microscopic section (Figure 1) showed epimyoepithelial islands containing altered ducts surrounded by lymphoid tissue, the characteristic features of Mikulicz' syndrome. Over the next few years the patient continued to complain of aching in the larger joints and in the back and noted progressive dryness of the mouth. Recently, at the age of 36, she had a severe bout of chills with fever, the temperature rising to 104° F. (40° C.). Generalized adenopathy and moderate splenomegaly were noted. The hemoglobin level was 9.8 gm. per 100 ml. of blood; leukocytes numbered 3,000 per cubic centimeter. No protein abnormalities were demonstrated by electrophoresis of serum, and responses to the LE preparation and to Latex agglutination tests were negative. Biopsy of an anterior cervical lymph node showed necrosis of the medullary arterioles with fibrin thrombi and perivascular neutrophilic infiltration, changes consistent with panarteritis.

Three months later the patient had another episode of spiking fever, associated with diffuse adenopathy and splenomegaly. The right parotid gland became grossly swollen and painful but the swelling subsided without specific treatment in four days.

For the six months preceding the time of this report the patient complained of dryness of the eyes and of progressive increase in the dryness of the mouth. Upon examination of the eyes with fluorescein, a few small superficial punctate staining areas were observed in the lower third of each cornea. Response to the Schirmer test was normal in each eye but electrophoresis of a tear sample revealed slight diminution of lysozyme, which may represent early involvement of the lacrimal glands. Use of methyl cellulose eye solution apparently relieved the ocular symptoms.

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